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Application of the Lithiation-Borylation Reaction to the Preparation of Enantioenriched Allylic Boron Reagents and Subsequent in situ Conversion into 1,2,4-Trisubstituted Homoallylic Alcohols with Complete Control over all Elements of Stereochemistry**

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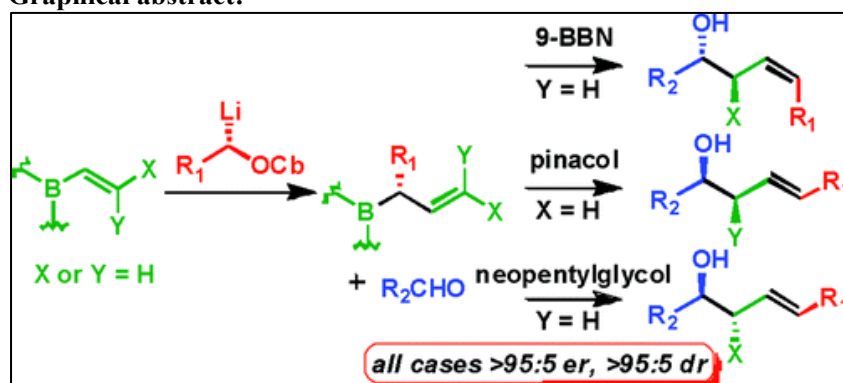
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Keywords:

Allyl Boration; Boronic Ester; Borane, Enantioselective; Lithiated carbamate

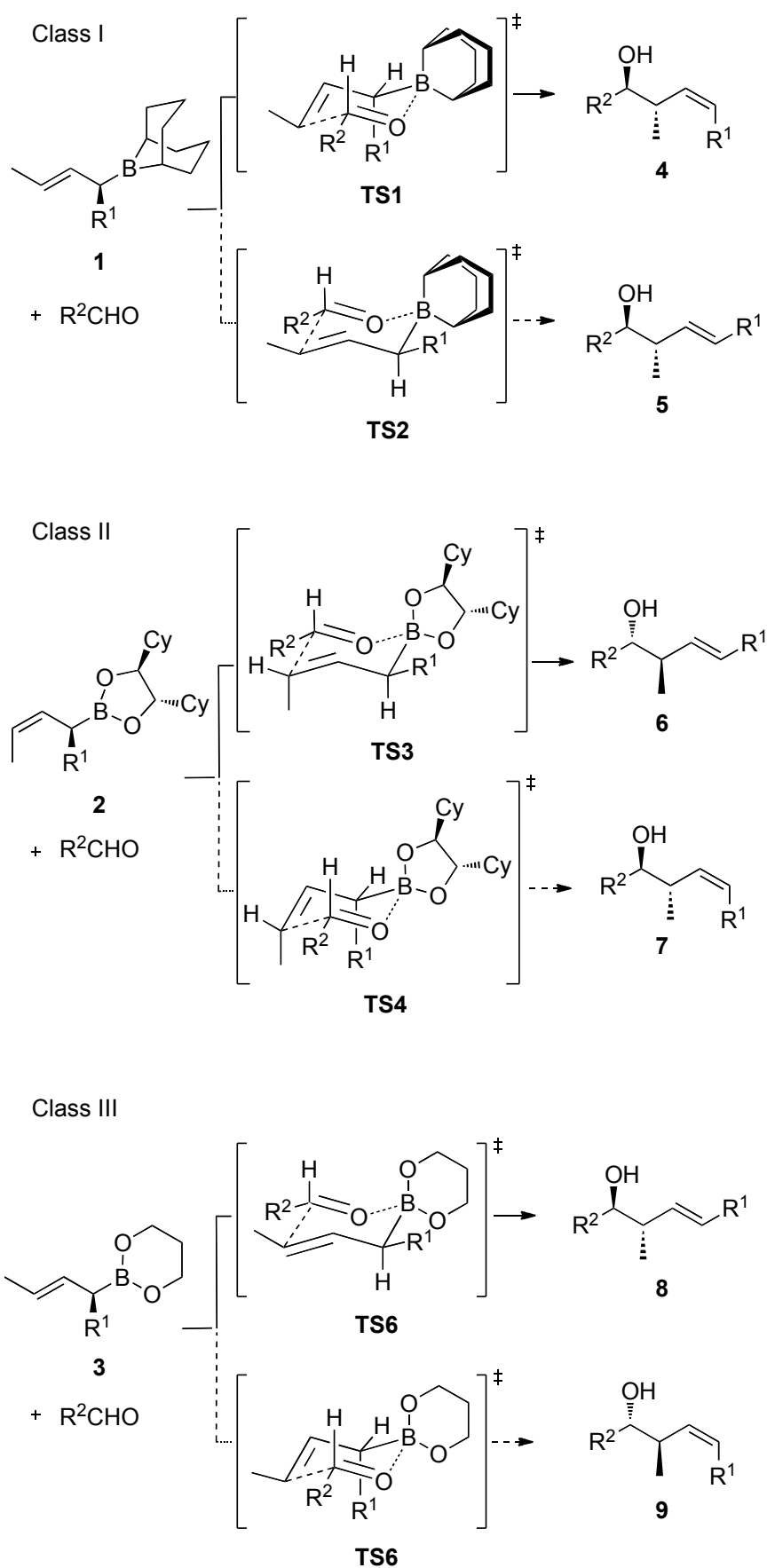
Abstract

The reactions of Hoppe's lithiated carbamates with vinylboranes and boronic esters give allylic boranes/boronic esters and subsequent addition of aldehydes provides a new route to enantioenriched homoallylic alcohols with high e.r. and d.r. Specifically, reactions of sparteine complexed lithiated carbamates with *trans*-alkenyl-9-BBN derivatives followed by addition of aldehydes gave (*Z*)-*anti*-homoallylic alcohols in greater than 95:5 e.r. and 99:1 d.r. However, in the special case of the methyl-substituted lithiated carbamate, diamine-free conditions were required to achieve high selectivity. Reactions of sparteine-complexed lithiated carbamates with (*Z*)-alkenyl-pinacol boronic esters and (*E*)-alkenyl neopentyl boronic esters gave (*E*)-*syn*- and (*E*)-*anti*-homoallylic alcohols respectively in greater than 96:4 e.r. and 98:2 d.r. In these reactions a Lewis acid (MgBr_2 or $\text{BF}_3\cdot\text{OEt}_2$) was required to promote both the 1,2-metallate rearrangement and the addition of the intermediate allylic boronic ester to the aldehyde. This methodology provides a general route to each of the three classes of homoallylic alcohols with high selectivity.

Introduction

The asymmetric allylboration of aldehydes is one of the most reliable and useful methods for making carbon-carbon bonds with control over relative and absolute stereochemistry.¹ In particular, Hoffmann's realization that relative stereochemistry could be controlled by the double bond geometry of crotylboronates² and Brown's discovery of highly enantioselective allylborations using pinane-derived reagents³ provided the foundations to this important reaction which continues to evolve to this date.⁴ The most notable recent developments include Hall's discovery that Lewis acids promote reactions of allylic boronic esters^{4a, 4b, 5}, Roush's use of bis-allylboron reagents for the stereocontrolled synthesis of 1,5-diols^{4c, 4d, 6} and the development of a new chiral allylborane by Soderquist which gives high enantioselectivity even with ketones.⁷

However, generally these powerful transformations are limited to simple allyl or crotylboron-reagents which ultimately lead to terminal alkenes; substitution in the α -position is considerably less common.⁸ We recognized that if we could prepare such reagents with control over enantioselectivity, then, by judicious choice of the *achiral* groups on boron and the initial double bond geometry we had the potential to control all the elements of stereochemistry of the homoallylic alcohol products at will [enantioselectivity, (*E/Z*)-stereochemistry and *syn/anti* stereochemistry] without the need for additional stereo-directing reagents (Scheme 1).

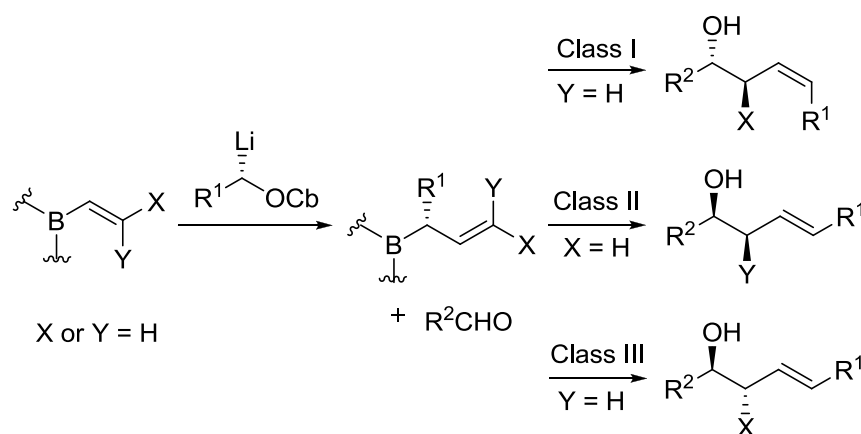


Scheme 1. Stereoselective aldehyde allylation using allylic boron reagents.

The high selectivity in such reactions originates from the closed chair transition-state structures involved and the basic need to minimize non-bonded steric interactions.^{2d, 9} For example, a hindered borane (e.g. 9-BBN¹⁰ as illustrated) or hindered boronic ester (e.g. tetraphenyl-1,2-ethanediol^{6, 11}) reacts *via* **TS1** since **TS2** suffers severe steric interactions between the equatorial substituent and the borane moiety (Scheme 1, class I). A *cis*-allylic boronic ester, which constitute the most commonly employed of the crotylboronic ester derivatives, react *via* **TS3** as **TS4** suffers severe A^{1,3} strain (Scheme 1, class II).^{2, 4d, 11a, 12} As this is the dominant interaction, steric hindrance between the equatorial substituent and boronic ester is tolerated, even if the boronic ester is moderately hindered e.g. pinacol, dicyclohexyl-1,2-ethanediol.² In contrast, *trans*-allylic boronic esters only give good selectivity if the boronic ester is unencumbered (e.g. 1,3-propanediol^{4c, 4d, 6}), enabling the reaction to occur *via* the less hindered **TS5** (**TS6** suffers a degree of A^{1,3} strain). Moderately hindered boronic esters e.g. pinacol boronic esters give low diastereoselectivity and usually in favor of the (*Z*)-isomer.^{12a}

Thus, each class of reagents has the potential to deliver high levels of relative stereocontrol but absolute control is not equally facile. The best known and utilized reagents are Hoffmann's (*Z*)-crotylboronic esters¹² which have been prepared in high e.r. using Matteson homologation.¹³ For class I^{9, 10a, 10b} and class III^{4c, 10c} reagents only sporadic examples for their generation in enantioenriched form exist.

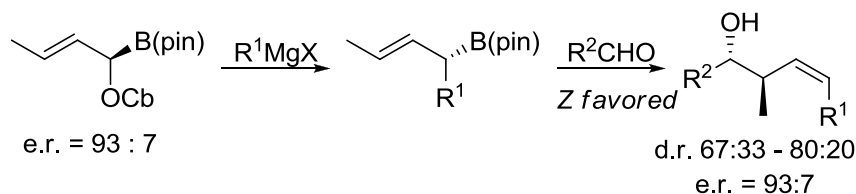
In this paper we describe a common general strategy to each class of these reagents which in the subsequent reactions with aldehydes leads to each class of homoallylic alcohols in >95:5 e.r. and >98:2 d.r. in all cases. Our common, general strategy involves the reactions of Hoppe's lithiated carbamates¹⁴ with appropriately substituted vinylboranes or boronic ester (Scheme 2).



Scheme 2. Synthesis of α -substituted allylic boron reagents and *in-situ* aldehyde allylation.

A conceptually related reaction had been reported by Hoppe (Scheme 3) in which an enantioenriched carbamoyl-substituted boronic ester was first reacted with a Grignard reagent and subsequent reaction with an aldehyde gave the homoallylic alcohol.¹⁵ However the d.r.s were only ~80:20, presumably because pinacol

esters had been used which only leads to low diastereoselectivity in the subsequent allylboration reaction and the e.r. was only 93:7 due to the source of the starting boronic ester.

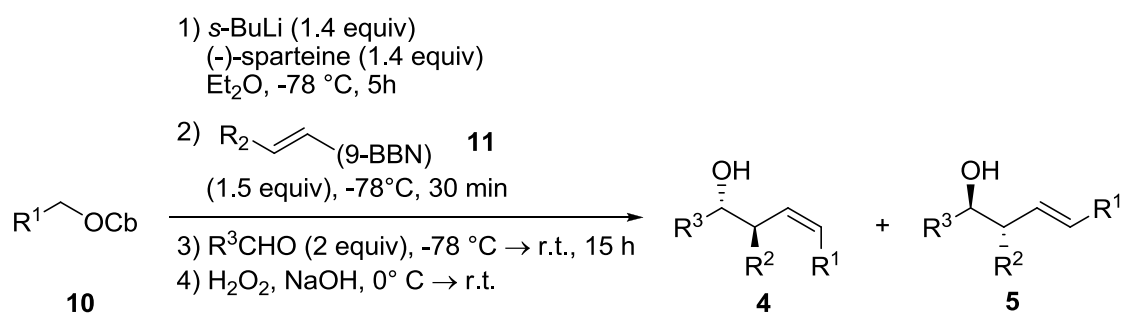


Scheme 3. Hoppe's synthesis of α -substituted allylic boronic esters and reaction with aldehydes.

Results and discussion

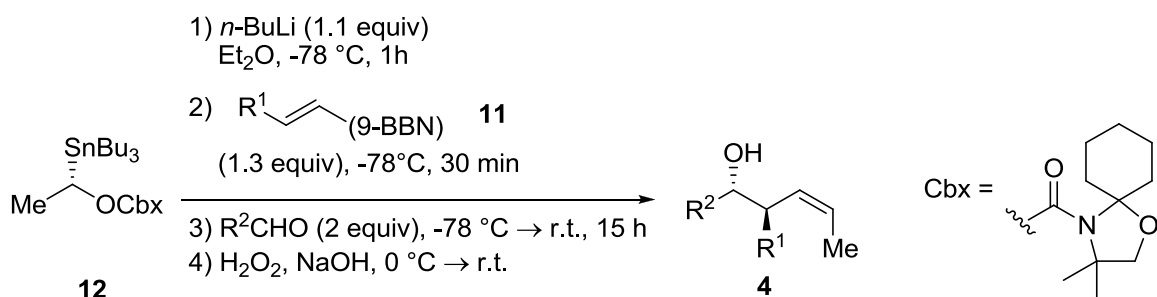
We began our investigations with the Class I reactions. The key intermediate allylboron reagents could potentially be prepared by the reaction of lithiated carbamates with vinylboranes or boronic esters.¹⁶ We had previously shown that α -aryl allylboranes bearing the 9-BBN group (Scheme 1, R^1 = Aryl) could be easily obtained through reaction of an aryl-stabilized sulfur ylide with a vinylborane and that the allylic borane generated reacted with aldehydes with high enantio- and diastereoselectivity.¹⁷ This reaction was limited to aryl-stabilized ylides; simple alkyl substituted ylides reacted with boranes with low enantioselectivity.¹⁸ However, more recently we have shown that lithiated alkyl-carbamates could react with boranes with high enantioselectivity.^{16b, 16c}

In extending this transformation to vinylboranes it was important that the conditions required for 1,2-metallate rearrangement did not result in isomerization of the labile allylic borane that was generated. We believed that this could be achieved by adding the aldehyde to the ate complex at low temperature. Upon warming, the ate complex would undergo a 1,2-metallate rearrangement giving the allyl borane which would be immediately trapped by the aldehyde before isomerization could occur. This protocol was found to be successful with a range of representative *trans*-vinylboranes, carbamates and aldehydes (Table 1, entries 1-9). In all cases high e.r. and perfect d.r. was observed except for the simplest carbamates (R^1 =Me, entries 10 and 11) which gave much lower e.r. This was surprising as we had previously found that the same carbamate reacted with B-Ph (9-BBN) with high e.r.¹⁶ After some experimentation we discovered that the diamine-free lithiated carbamate generated from the corresponding stannane¹⁹ **12** rescued this important substrate giving the homoallylic alcohol with excellent e.r. and perfect d.r. for a range of aldehydes and alkenyl 9-BBN derivatives (Table 2).²⁰



Entry	R ¹	R ²	R ³	Yield 4 (%)	e.r. (4)	d.r. (4:5)
1	Ph(CH ₂) ₂	Me	Cy	84	96 : 4	>99 : 1
2	Ph(CH ₂) ₂	Me	Ph	82	97 : 3	>99 : 1
3	Ph(CH ₂) ₂	Bu	Ph	91	98 : 2	>99 : 1
4	Ph(CH ₂) ₂	Bu	Cy	78	98 : 2	>99 : 1
5	Ph(CH ₂) ₂	CH ₂ OSiMe ₃	Ph	73	98 : 2	>99 : 1
6	Ph(CH ₂) ₂	Me	Bu	80	98 : 2	>99 : 1
7	<i>i</i> -Pr	Me	Ph	58	98 : 2	>99 : 1
8	<i>i</i> -Pr	Me	Cy	54	96 : 4	>99 : 1
9	<i>i</i> -Pr	Bu	Ph	60	95 : 5	98 : 2
10	Me	Me	Ph	88	60 : 40	>99 : 1
11	Me	Me	Cy	65	88 : 12	> 99 : 1

Table 1. Aldehyde allylation using α-substituted-allyl-(9-BBN) reagents



Entry	R ¹	R ²	Yield 4 (%)	e.r. (4)	d.r. (4:5)
1	Me	Ph	84	95 : 5	>99 : 1
2	Me	Cy	78	94 : 6	>99 : 1
3	Bu	Ph	64	93 : 7	>99 : 1

Table 2. Diamine-free aldehyde allylation using α-stannylated *O*-ethyl-carbamate

The high diastereoselectivity observed in the allylation reaction can be rationalized by the increased steric encumbrance in transition-state structure **TS2** compared to **TS1** (Figure 1).^{5a, 9, 21} Severe hindrance between the 9-BBN ring and R¹ would force the α-carbon substituent into a pseudo-axial position resulting in the *anti*-diastereoisomer and (*Z*)-alkene geometry.

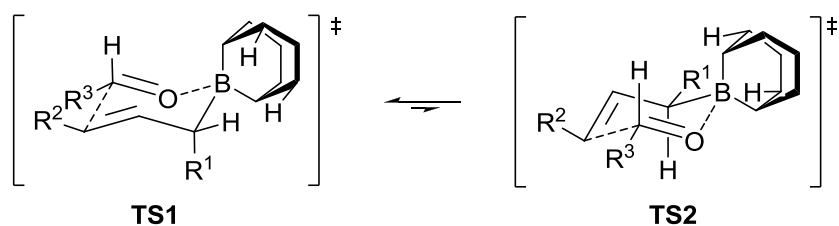
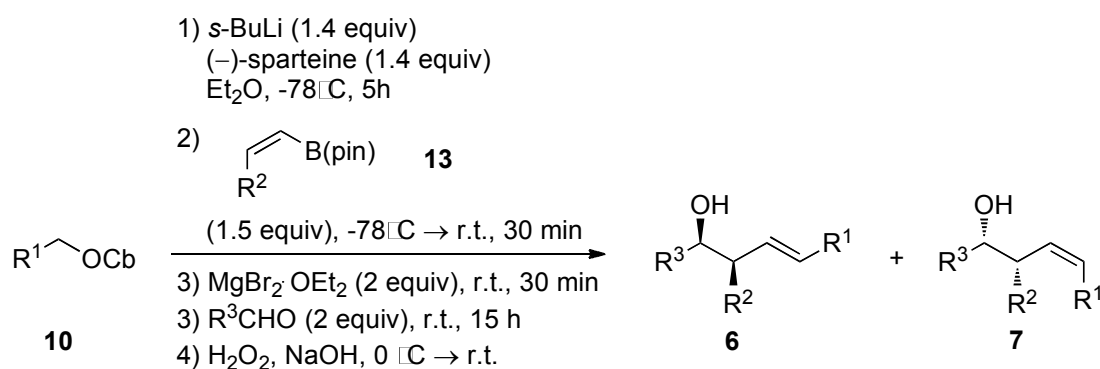


Figure 1. Competing transition-state structures in the addition of α -substituted allyl-(9-BBN) reagents to aldehydes.

In order to target class II reactions we chose *cis*-vinyl pinacol boronic esters, which were easily prepared by esterification of commercially available vinylboronic acids. In this case the presence of the boronic ester in place of the borane presents additional challenges: (i) the 1,2-metallate rearrangement is now much slower and (ii) the allylic boronic ester is much slower at allylboration. Fortunately, both processes can be accelerated with Lewis acid catalysis.^{5a, 22} After optimization of the reaction conditions a protocol was developed which showed broad generality for a representative range of boronic esters, aldehydes and carbamates leading to the (*E*)-*syn*-homoallylic alcohol with high d.r. and e.r. in all cases (Table 3).



Entry	R ¹	R ²	R ³	Yield 6 (%)	e.r. (6)	d.r. (6:7)
1	Ph(CH ₂) ₂	Bu	Ph	54	99 : 1	>99 : 1
2	Ph(CH ₂) ₂	Me	Ph	46	99 : 1	>99 : 1
3 ^a	Ph(CH ₂) ₂	Me	Cy	59	99 : 1	>99 : 1
4	Me	Me	Ph	56	99 : 1	>99 : 1
5 ^a	Me	Me	Cy	46	99 : 1	>99 : 1

(a) 4 equivalents of MgBr₂·OEt₂ used.

Table 3. Aldehyde allylation using (*Z*)-allylic boronic esters.

The stereochemical outcome can be rationalized by considering the Lewis acid-activated closed TS for the reaction. In this case the *cis* R² substituent imposes severe A^{1,3} strain and so forces R¹ into a pseudo-equatorial position **TS8** thus leading to the (*E*)-*syn*-isomer (Figure 2).

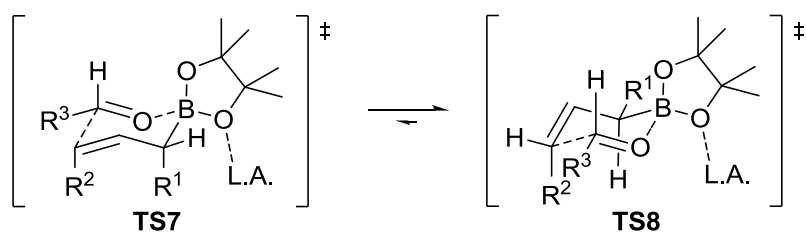


Figure 2. Stereoselectivity of (*Z*)-allylic-boronic esters.

In order to obtain the (*E*)-*anti*-isomer we would ‘simply’ require the (*E*)-allylic boronic ester. However, this is one of the most challenging diastereoisomers to prepare selectively since the two competing closed transition-state structures both suffer from different forms of steric interactions (Figure 3): **TS9** suffers from $A^{1,3}$ interactions between R^1 and the vinyl proton whilst **TS10** suffers from steric hindrance between R^1 and the boronic ester diol group.

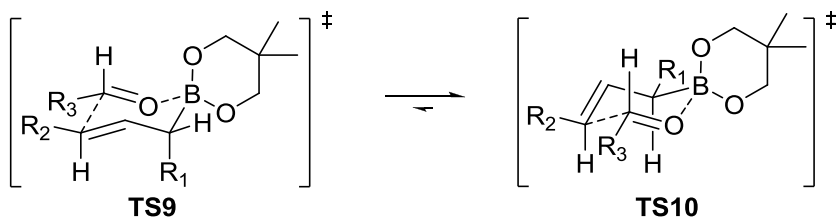
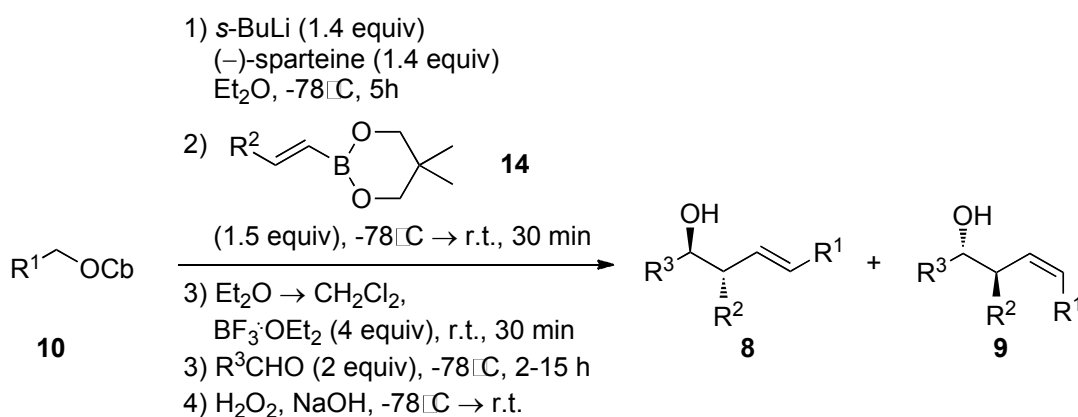


Figure 3. Stereoselectivity within the allylation reaction using (*E*)-allylic-boronic esters.

In order to favor **TS10** we required an unhindered boronic ester and so chose the neopentyl boronic ester for the Class III reactions. These boronic esters have similar steric hindrance to propane-1,3-diol boronic esters, but are more robust and can even be purified by silica gel chromatography in many cases. These were easily prepared by hydroboration of an alkyne with HBBR_2 followed by addition of neopentyl glycol.²³ After some experimentation a general protocol was again found that gave moderate to high yields, high e.r. and very high d.r. in this most challenging of cases. The optimum conditions involved addition of the boronic ester to the lithiated carbamates followed by solvent exchange ($\text{Et}_2\text{O} \rightarrow \text{CH}_2\text{Cl}_2$), addition of $\text{BF}_3 \cdot \text{OEt}_2$ (4 equiv.) at room temperature, cooling to -78°C , addition of the aldehyde and quenching at -78°C , after completion of the reaction. We believe the excess Lewis acid is required as some is sequestered by the diamine and LiOCb which are present in the reaction mixture. Without the solvent exchange, the reaction times are considerably longer.²⁴ Under the optimized conditions a representative range of carbamates, *trans*-vinylboronic esters and aldehydes all gave excellent results (Table 4).



Entry	R ¹	R ²	R ³	Yield 8 (%)	e.r. (8)	d.r. (8:9)
1	Ph(CH ₂) ₂	Me	Ph	67	98 : 2	>99 : 1
2	Ph(CH ₂) ₂	Me	Cy	60	98 : 2	>99 : 1
3	Ph(CH ₂) ₂	Bu	Ph	58	99 : 1	>99 : 1
4	Ph(CH ₂) ₂	Bu	Cy	67	99 : 1	>99 : 1
5	Me	Me	Ph	51	95 : 5	>99 : 1
6	Me	Me	Cy	58	99 : 1	>99 : 1

Table 4. Allylation of aldehydes using (*E*)-allylic boronic esters.

Conclusion

In conclusion, we have developed a general and convergent protocol for combining lithiated carbamates, vinylboranes/boronic esters and aldehydes to give 1,2,4-substituted homoallylic alcohols with control over relative and absolute stereochemistry. The absolute stereochemistry is controlled through sparteine-mediated lithiation of the carbamate; a reaction where the other enantiomer is also easily accessible through the use of the (+)-sparteine surrogate.²⁵ The relative stereochemistry is controlled by the nature of the boron substituent and the geometry of the initial vinylboron reagent: (i) the hindered 9-BBN combined with (*E*)-vinylborane leads to the (*Z*)-*anti*-isomer (class I), (ii) the relatively hindered pinacol boronic ester combined with the (*Z*)-vinylboronic ester leads to the (*E*)-*syn*-isomer (class II), (iii) the unhindered neopentyl boronic ester combined with the (*E*)-vinylboronic ester gives the (*E*)-*anti*-isomer (class III). The new processes described significantly expand the scope of allylboron reactions as it not only introduces substitution in the alkene of the homoallylic alcohol product with control of double bond geometry, but also achieves exquisite levels of stereocontrol. The predictable stereochemical outcome and ease of access to the reagents are features that readily lend this protocol to use in complex natural product synthesis. Studies in this area are ongoing.

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